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Cystic changes in fetal kidneys following ureteral ligation: Studies by microdissection

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Cystic changes in fetal kidneys following ureteral ligation: Studies by microdissection. Intrauterine ureteral ligation of fetal rabbits is followed by the development of dilatation of collecting ducts and dilatation or cyst formation in nephrons in the obstructed kidneys or both. Microdissection reveals the presence of cysts in various portions of the nephron, the most striking being localized in the loop of Henle and, particularly, at the bend of the loop. The cysts of the loop of Henle in fetal rabbit kidneys are similar to those so frequently encountered in microdissection studies of human cystic kidneys. The unquestioned relationship of the experimental cysts to pressure effects gives insight into one mechanism for the causation of the human cysts. The cysts of loop of Henle which occur in the presence of urinary tract obstruction in human kidneys are readily explained. In the absence of urinary tract obstruction, however, the cysts of nephrons of certain human kidneys may result from local obstruction to individual nephrons by pressure of contiguous cysts of collecting ducts.

Modifications kystiques des reins de foetus consécutives à la ligature urétérale: Etude par microdissection. La ligature urétérale intra-utérine chez le foetus de lapin est suivie du développement de dilatations des canaux collecteurs et de dilatations et/ou de formations kystiques des néphrons du rein obstrué. La microdissection révèle la présence de kystes dans diverses portions du néphron, les plus nets sont localisés à l'anse de Henle et, particulièrement, à la pointe de l'anse. Les kystes de l'anse de Henle, dans le rein foetal de lapin, sont semblables à ceux très fréquemment observés dans les études par microdissection des reins humains kystiques. La relation non explorée entre les kystes expérimentaux et les conséquences de l'hyperpression permet d'aborder un mécanisme générateur des kystes humains. Les kystes de l'anse de Henle qui surviennent en présence d'obstacles de l'appareil excréteur sont facilement explicables. Cependant, en l'absence d'obstacle, les kystes des néphrons de certains reins humains peuvent être la conséquence d'une obstruction locale des néphrons individuels par la pression de kystes contigus des canaux collecteurs.

The frequent coexistence of urinary obstruction and renal dysplasia in human patients has stimulated a number of attempts to produce renal dysplasia in experimental animals by the artificial creation of obstructive urinary tract lesions [1–4]. No one, to our knowledge, has produced unequivocal dysplastic lesions in such experiments, although epithelial changes similar to those encountered in human renal dysplasia have been observed in certain instances [1, 3, 4].

One of us (M.M.R.) recently developed an operative technique by means of which ligation of the ureter of fetal rabbits *in utero* could be accomplished with a high rate of survival. The intent of the original experiments was to produce multicystic kidneys ("total dysplastic kidneys"). Although gross and microscopic alterations were discernible in the fetal rabbit kidneys following ureteral ligation, changes suggestive of dysplasia were not encountered.

The presence of many cysts or dilated nephrons, tubules or collecting ducts in the test kidneys, or all of these, suggested, however, that the intrauterine ureteral ligation models might be of interest in the elucidation of the pathogenesis of renal cysts that form in response to urinary back pressure. It was felt that the Oliver technique for microdissection of the nephron and collecting ducts could be profitably applied to these obstructed kidneys to accurately determine the location of the cysts.

Accordingly, a number of intrauterine ureteral ligations in fetal rabbits were performed, and the resultant cystic changes studied by microdissection, in addition to the usual gross and histologic methods.

Methods

Ten fetal rabbits in which unilateral intrauterine ureteral ligation was performed successfully were killed at intervals after ligation varying from two to

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Table 1. Occurrence and distribution of cysts in population of nephrons and collecting ducts studied by microdissection in fetal rabbit kidneys after ureteral ligation

Identification No.	Duration of ligation, *Days*	Gestational age[a] at time of ligation, *Days*	Glomeruli	Proximal tubules	Loops of Henle			Distal convoluted tubules	Collecting ducts	Remarks
					Desc. Limbs	Bend-Angle	Asc. Limbs			
MD378	2	24	1% Cystic	0	0	0	0	1% Show minimal change	Slightly dilated	
MD376	2	29	15% Cystic	5% Show minimal change[b]	5% Cystic	10% Cystic	5% Cystic	5% Cystic	Slightly dilated	Littermate of MD377
MD377	2	29	15% Cystic	5% Show minimal change	5% Cystic	10% Cystic	5% Cystic	5% Cystic	Slightly dilated	
MD373	4	23	5% Cystic	5% Show minimal change	10% Cystic	50% Cystic	10% Cystic	5% Show minimal change	Dilated	Littermate of MD374
MD374	4	23	5% Cystic	5% Show minimal change	10% Cystic	55% Cystic	10% Cystic	5% Show minimal change	Dilated	
MD379	7	22	50% Cystic	5% Show minimal change 1% cystic	10% Cystic	30% Cystic	10% Cystic	10% Cystic	Dilated	Littermate of MD380
MD380	7	22	50% Cystic	20% Cystic	10% Cystic	20% Cystic	10% Cystic	10% Cystic	Dilated	
MD375	7	25	10% Cystic	5% Show minimal change	5% Cystic	25% Cystic	5% Cystic	5% Show minimal change	Dilated	
MD381	10	19	40% Cystic	25% Cystic	15% Cystic	20% Cystic	15% Cystic	15% Cystic	Dilated	
MD382	10	19	25% Cystic	25% Cystic	15% Cystic	30% Cystic	20% Cystic	10% Cystic	Dilated	

[a] Normal gestational period in rabbit is 31 to 32 days.
[b] "Minimal change" refers to dilatation as seen in proximal tubules of nephrons *A* and *C* in Fig. 4, and two of proximal tubules in Fig. 8.

ten days (Table 1). The gestational age at ligation varied from 19 to 29 days. Usually, those ligated earlier in gestation were also those with the longest periods of ligation. The unoperated contralateral kidneys from each of the fetuses were considered to be controls.

The kidneys were fixed in 10% neutralized formaldehyde-saline solution for at least 21 days and then halved sagittally, following fixation. Histologic sections were made of each test kidney, but at least one-half of each was available for microdissection studies.

Microdissection of blocks from all ten test kidneys and the ten contralateral control kidneys was carried out by the method of Oliver, MacDowell and Tracy [5, 6]. From 200 to 500 nephrons were dissected out from each test kidney, and no less than 200 from each control kidney. When appropriate, mosaic photomicrographs were made of isolated nephrons and collecting ducts.

Results

The gross changes in the test kidneys were quite like those described previously [2]. The obstructed kidneys were enlarged (Fig. 1). When the obstructed kidneys were sectioned, fluid escaped. The papillae of the obstructed kidneys were effaced, and the pelves presented varying degrees of dilatation.

Histologic sections of the test kidneys revealed thinned, compressed renal parenchyma (Fig. 2*A*). Test and control kidneys displayed subcapsular

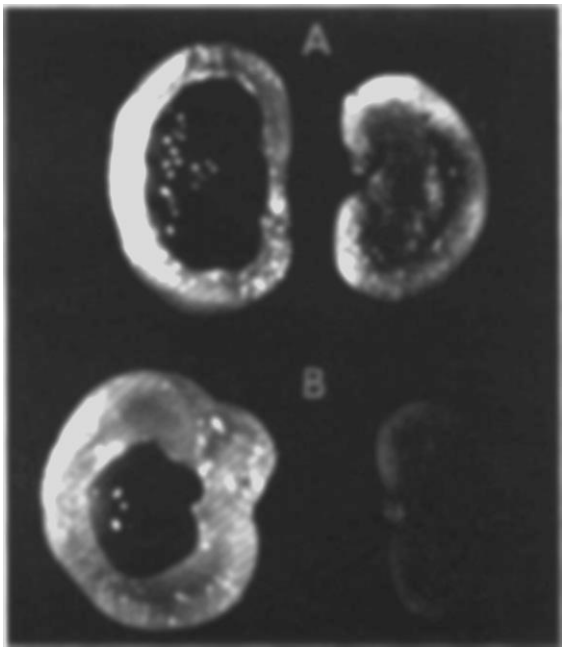

Fig. 1. *A*: Left, *sagittal cut surface of obstructed left kidney (MD377), killed two days following ureteral ligation.* Right, *cut surface of right (control) kidney, same animal. B*: Left, *sagittal cut surface of obstructed left kidney (MD380), obtained seven days following ligation.* Right, *half of right (control) kidney, same animal* (× 2.5).

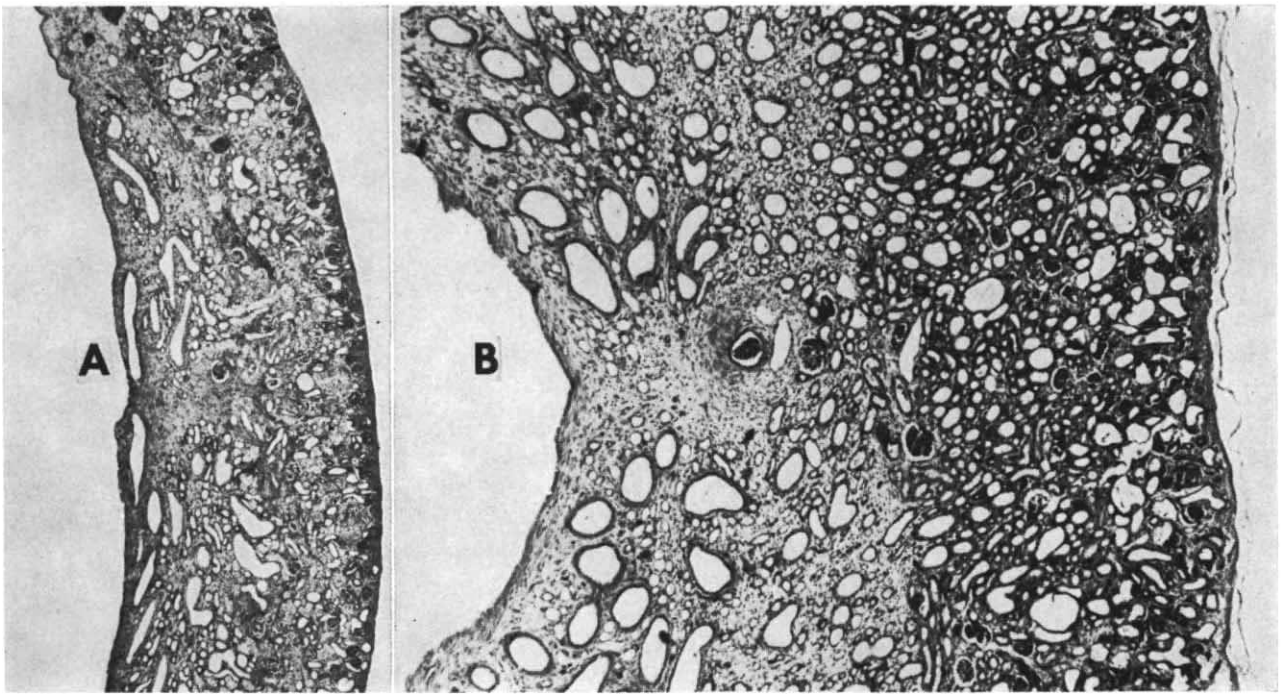

Fig. 2. *A*: *Photomicrograph of section of thinned compressed parenchyma of obstructed kidney MD373; duration of ligation, four days* (×*28*). Cross-sections of dilated or cystic ducts and nephrons are seen. *B*: *Photomicrograph of section of compressed renal substance of test kidney MD380, examined after seven days' ligation* (×*75*). The largest, most dilated structures are collecting ducts.

nephrogenic zones. A few small glomerular cysts were noted in sections of the test kidneys. These tended to be more numerous in the kidneys in which the duration of ligation had been seven or ten days. Dilated cystic ducts and tubules were also apparent in the sections (Figs. 2*A* and *B*). The number of cysts varied in the several test kidneys, there being few in the kidneys of animals killed two days following ligation, and many more in the kidneys in which obstruction had been in effect for from four to ten days.

We encountered no cysts in sections of the control kidneys.

Microdissection studies. It is noteworthy that all of the nephrons that presented any type of dilatation or cystic change or both originated in the outer half of cortex.

1. Glomeruli. The occurrence and distribution of cysts in the test kidneys, as determined by microdissection, are detailed in Table 1. All ten kidneys displayed Bowman's capsule cysts of varying degrees of frequency. Some were minimal halo-like dilatations of Bowman's capsules (Fig. 3*B*). Others were more striking, as in Figs. 5*A* and 5*D*. None was large. Many more glomeruli showed this change in the kidneys in which the interval between ligation and study was at least seven days.

2. Proximal convoluted tubules. Striking dilatation or cyst formation was present in proximal tubules only in three of the last four kidneys in the series, i.e., one of those killed seven days after ligation, and both of those killed ten days after ligation. In those kidneys in which the duration of ligation was but two days, proximal tubular involvement was absent in one and minimal in two. No more than minimal change, if any, was noted in the two kidneys in which the duration of ligation was four days. More conspicuous changes, as exemplified in kidneys ligated for seven or ten days, are shown in the mosaic photomicrographs of Fig. 3. Here the cysts were localized and discrete. Continuity of cysts of proximal tubules and descending limbs within individual nephrons may be seen in Figs. 6*C* and *D*.

3. Loop of Henle. Two of the kidneys in which the duration of ligation was but two days displayed cysts within the loops. These were in nephrons originating in outermost cortex. No more than 10% of loops dissected in these two kidneys were cystic. The third kidney with a two-day duration of ligation showed no involvement of Henle's loops. The kidneys in which the duration of ligation was four, seven and ten days displayed striking and extensive cystic change in Henle's loops. The two with four days of ligation

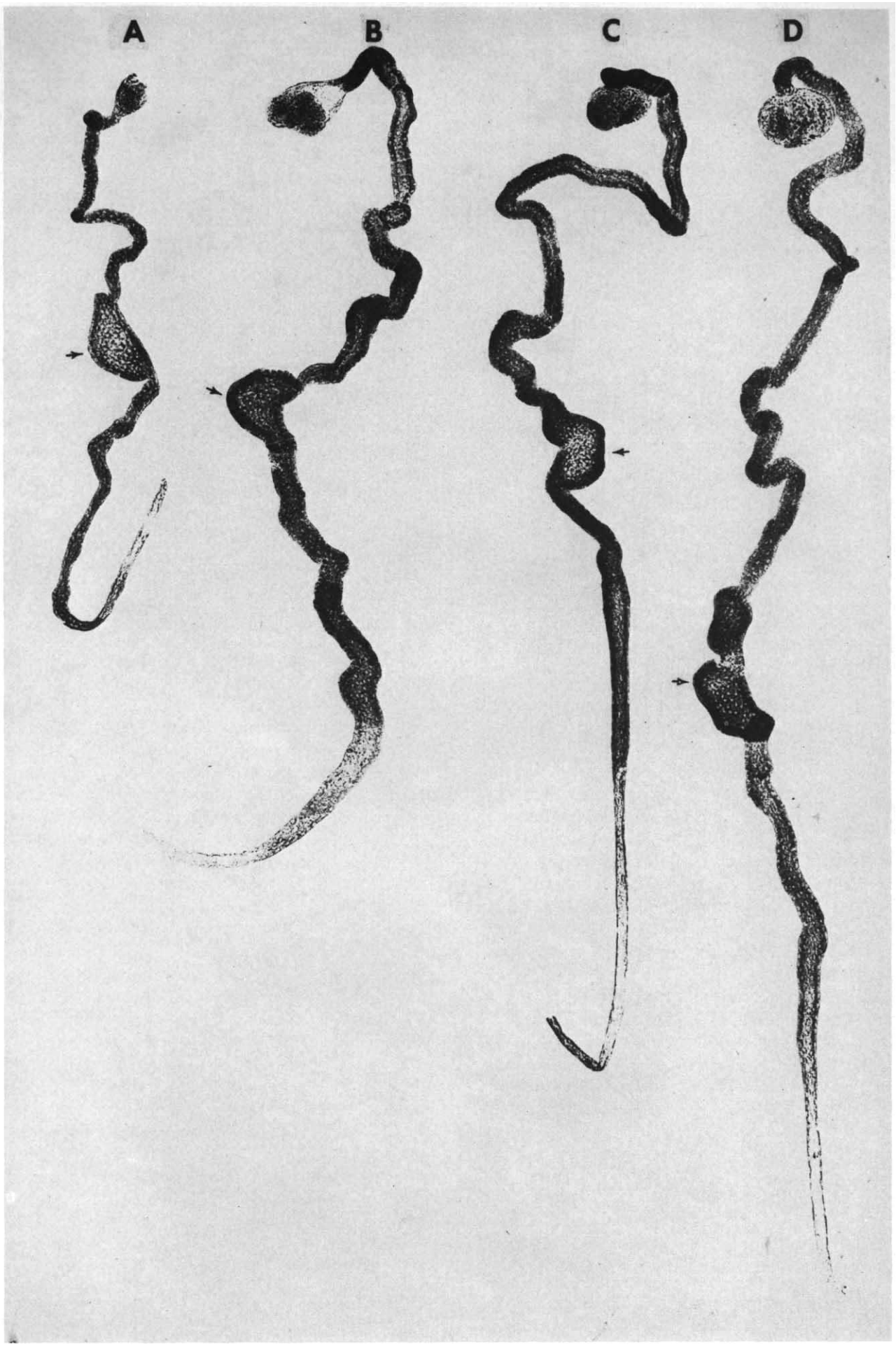

Fig. 3. *Mosaic photomicrographs of four of the proximal tubules dissected from test kidney MD382; duration of ligation, ten days (reduced to ×82 from ×200).* Glomerulus of nephron *B* shows dilatation of Bowman's capsule. All four tubules present focal dilatations which may be regarded as cysts.

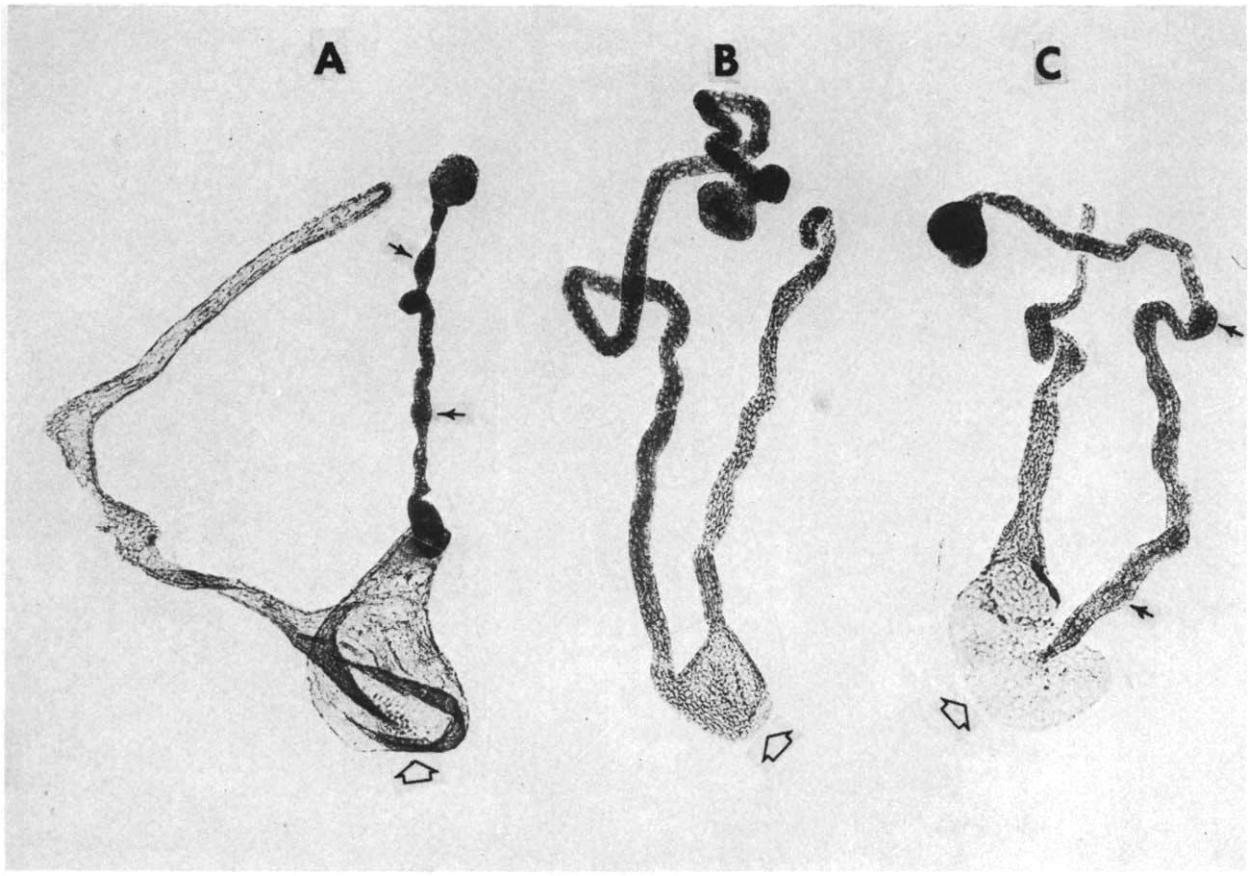

Fig. 4. *Mosaic photomicrographs of three of the nephrons dissected from obstructed kidney MD374; duration of ligation, four days (reduced to × 83 from × 200).* Nephrons *A* and *C* reveal some proximal tubular irregularity (marked with *arrows*) but the cysts of the bend or angle of the loop of Henle are most conspicuous. The bends are marked by open *arrows*. In nephron *A* the ascending limb of Henle's loop is also dilated. In nephron *B* the cyst of the bend does not present thinning and stretching of the cells, but the cysts of bends in nephrons *A* and *C* do.

displayed cysts of the bend[1] in 50 and 55% of the loops surveyed. In the kidneys with either seven or ten days of obstruction, 20 to 30% of the loops displayed cysts at the bend.

As shown in Table 1, many loops of Henle displayed cystic enlargement of descending or ascending limbs. These were in some instances continuous with cysts of the bend of the loop.

The cysts of the loop of Henle appeared in most instances to be the result of passive dilatation, with stretching and elongation of cell outlines. The walls appeared thin. The earliest change, to judge from its prevalence in the two- and four-day ligations, was the cystic dilatation at the bend of the loops of Henle (Figs. 4, 5*B* and *C* and 8). Those kidneys in which duration of ligation was seven or ten days displayed fewer cysts confined to the bend, but many more presented extension of cysts from the bend into ascending or descending limbs or both than in the four-day ligation animals (Figs. 5*A* and *D*, 6).

4. Distal convoluted tubules. Cysts of the distal convoluted tubules were present in from 5 to 15% of the population of nephrons observed in six of the ten kidneys studied (Fig. 5*D* and 6*B*, *C* and *D*). These were often continuous with cysts of ascending limbs.

5. Collecting tubules. The collecting ducts in each of the test kidneys presented symmetrical continuous dilatation. The largest tubular structures demonstrated, either by histologic means or microdissection, were the first few branches of the collecting system. A comparison with the normal is seen in Fig. 7. Several generations of collecting ducts with some of nephrons attached to most distal branches are shown in Fig. 8.

Discussion

In these experiments, we are dealing with a relatively simple stimulus to cyst formation, i.e., the ligation of a ureter. The short duration of the experiments, with

[1] The abrupt hairpin turn of the loop of Henle will be referred to as the "bend" except when quoting authors who have adopted other terms for it, such as the "angle" or the "crest."

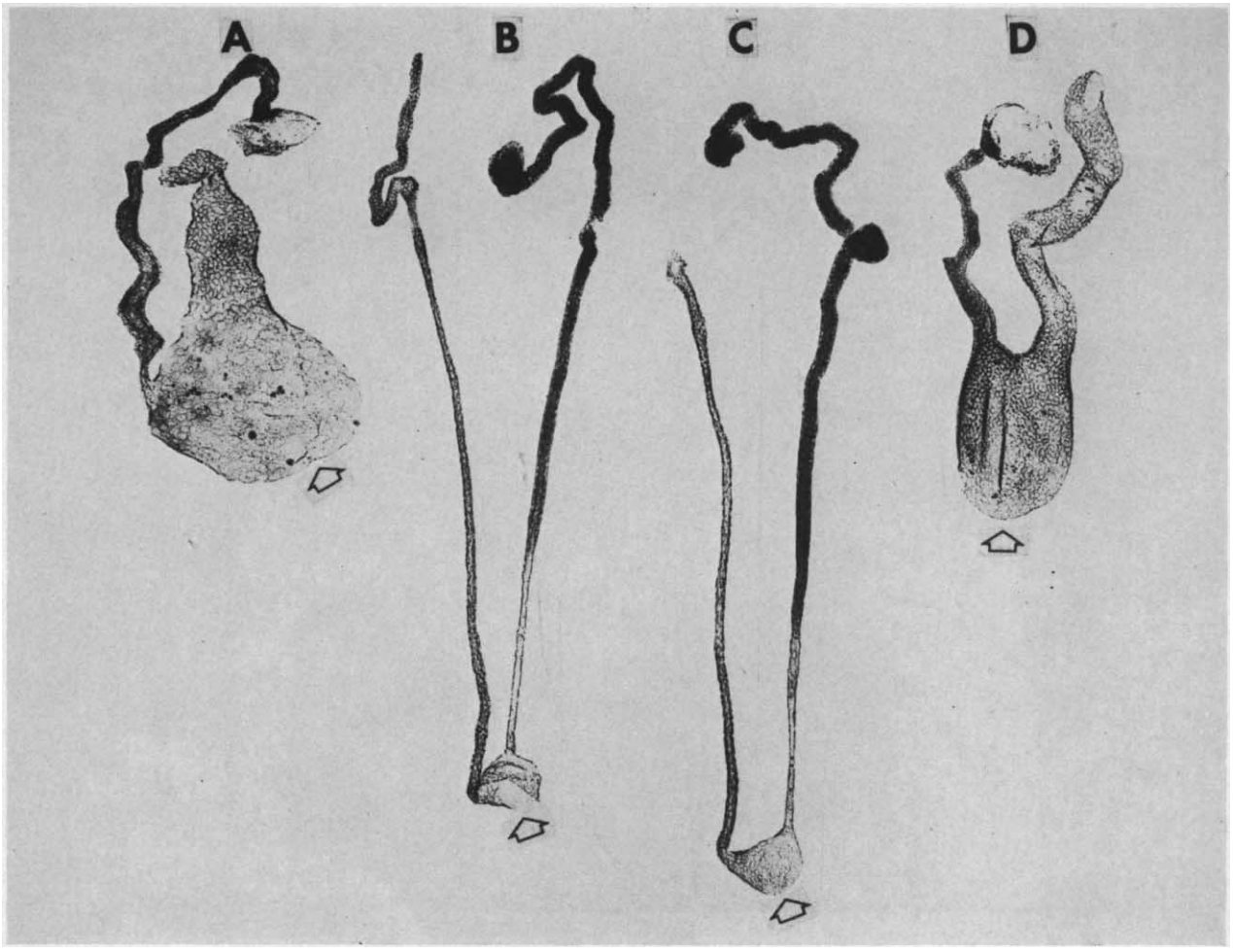

Fig. 5. *Mosaic photomicrographs of four of nephrons dissected from obstructed kidney of MD379, duration of ligation seven days (reduced to* $\times 64$ *from* $\times 200$*).* Nephrons *A* and *D* are immature, from the subcapsular area. Each shows dilatation of Bowman's capsule. The cysts in both *A* and *D* extend from the bend of the loop of Henle up into the ascending limb. Bends are indicated by *open arrows*. Nephrons *B* and *C*, older and more mature, present small cysts of the bend or angle of Henle's loop. The thin segment of loop is identifiable in the descending limb of both *B* and *C* nephrons.

none lasting over ten days, minimized the effects of other forces, stimuli or noxae secondary to the ligation. Thus, the impetus to cyst formation is provided only by an increase in intraluminal pressure.

The experiments were productive in that cysts in large numbers were produced in the nephrons of the ligated fetal rabbit kidneys. That the cysts were confined to the nephrons originating in the outer half of the kidney is of considerable interest, since the outermost nephrons in a mammalian kidney are the youngest. This distribution of the cysts may, therefore, be related to the relative immaturity of these newer nephrons.

In the experiments of Strong involving ureteral ligation in adult rabbits [7], little in the way of dilatation or cystic change was observed other than in the distal convoluted tubules, connecting pieces and collecting ducts. Although extensive microdissection was utilized in this study by Strong, cysts of Henle's loops were not observed. Thus, it is apparent that the results of ureteral ligation are quite different in fetal and adult rabbit kidneys.

Beck has reported experiments in fetal lambs in which ureteral obstruction was accomplished either during the first half or the last half of gestation [3]. In the animals ligated before 70 days of gestation, in which contralateral nephrectomy was also performed, it is stated that "polycystic disease" was produced in the obstructed kidney. No microdissections were performed. In those animals ligated following 80 days of gestation, changes in histological sections similar to those observed to occur in mature animals were described. Beck states that "the gestational age is obviously of critical importance in determining the results of intrauterine urinary obstruction" [3].

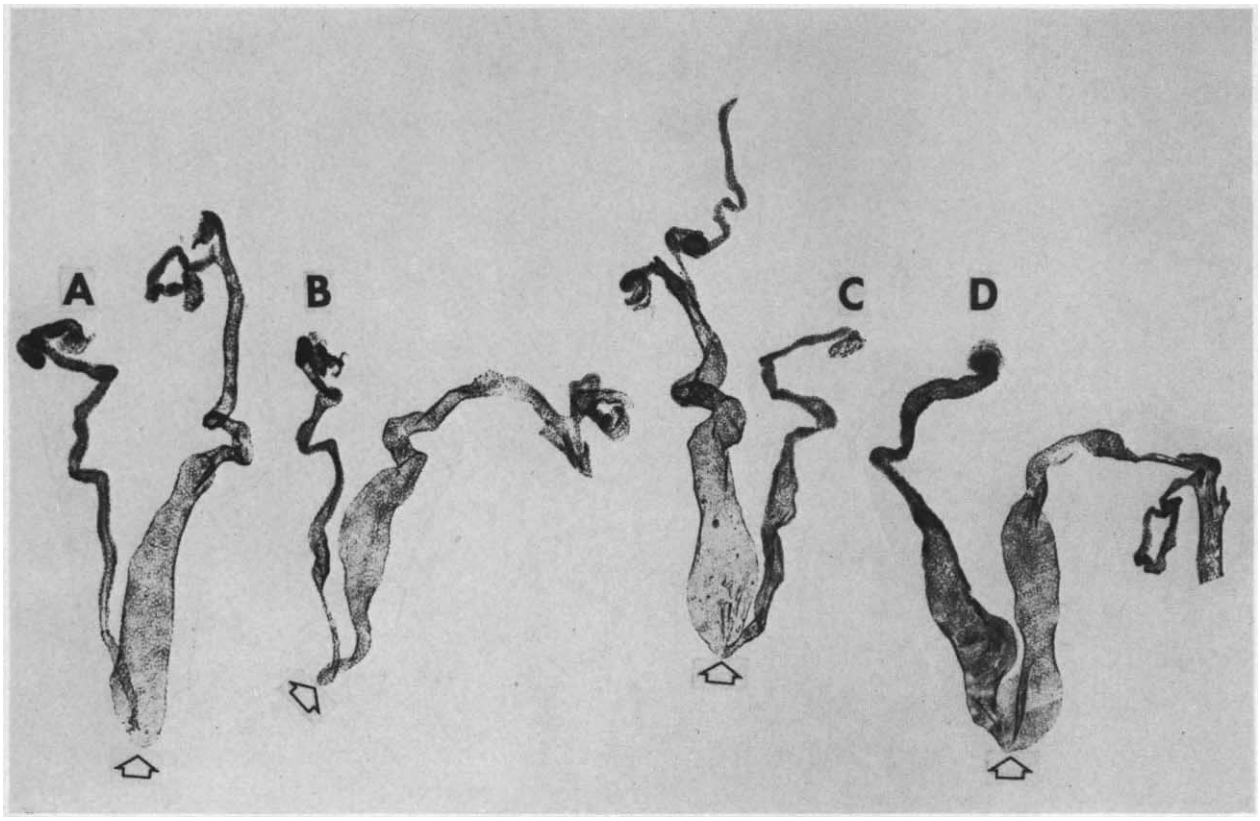

Fig. 6. *Mosaic photomicrographs of four of the nephrons dissected from test kidney MD381; duration of ligation, ten days (reduced to* $\times 45$ *from* $\times 200$*).* Nephron *A* presents a cyst extending from bend through ascending limb of Henle. Bends are marked with *open arrows*. The cyst in nephron *B* extends from the bend through the ascending limb to involve distal convoluted tubule. The cysts of *C* and *D* involve the entire loop of Henle and the distal convoluted tubules.

Tanagho reported experiments in which partial ureteral obstruction was created in seven fetal lambs at 70 to 75 days' gestation [4]. Cystic dilatation of renal tubules and dilatation of Bowman's capsules were noted. Identification of tubules by microdissection was not attempted.

Shimamura, Kissane and Gyorky reported on a study in which ureteral obstruction was effected in adult rats to produce experimental hydronephrosis [8]. They noted minimal changes in the distal convoluted tubules and loop of Henle. Microdissection was included in the techniques applied to this study.

Osathanondh and Potter [9] have theorized that the susceptibility of the nephrons of immature kidneys to back pressure may be related to the fact that the collecting tubules are at this stage "short and almost straight." Conversely, they state that when back pressure is exerted by urethral or ureteral obstruction in an adult kidney, "the renal pelvis, calyces and papillary ducts feel the greatest effect and become dilated first, and to a greater extent than any other portions of the kidney. Because of their length and tortuosity, nephrons seldom become cystic." These opinions and observations of Osathanondh and Potter are in reference to human kidneys.

In examining the changes occuring in the test kidneys subsequent to obstruction, we were most impressed by the cysts in the loops of Henle, and particularly those occupying the bends in those loops. In the kidneys of the fetuses in which the duration of ureteral ligation has been four, seven or ten days, cysts of the bends in loops of Henle were present in from 20 to 55% of the population of nephrons studied.

These cysts and the contiguous cysts or separate cysts in the ascending or descending branches of the loops, or in both, tended to overshadow the cysts in other units of nephrons.

One wonders if there is not a predilection for the loops, as the sites of cysts, and particularly the bends of the loops. In nearly every test kidney, the bend of the loop displayed as many or more cysts than any other portion of the nephrons.

Careful examination of the bend of loops of Henle in mosaic photomicrographs of several immature human nephrons in Oliver's *Nephrons and Kidneys* [10] will reveal that the bend of the loop may be bulbous at

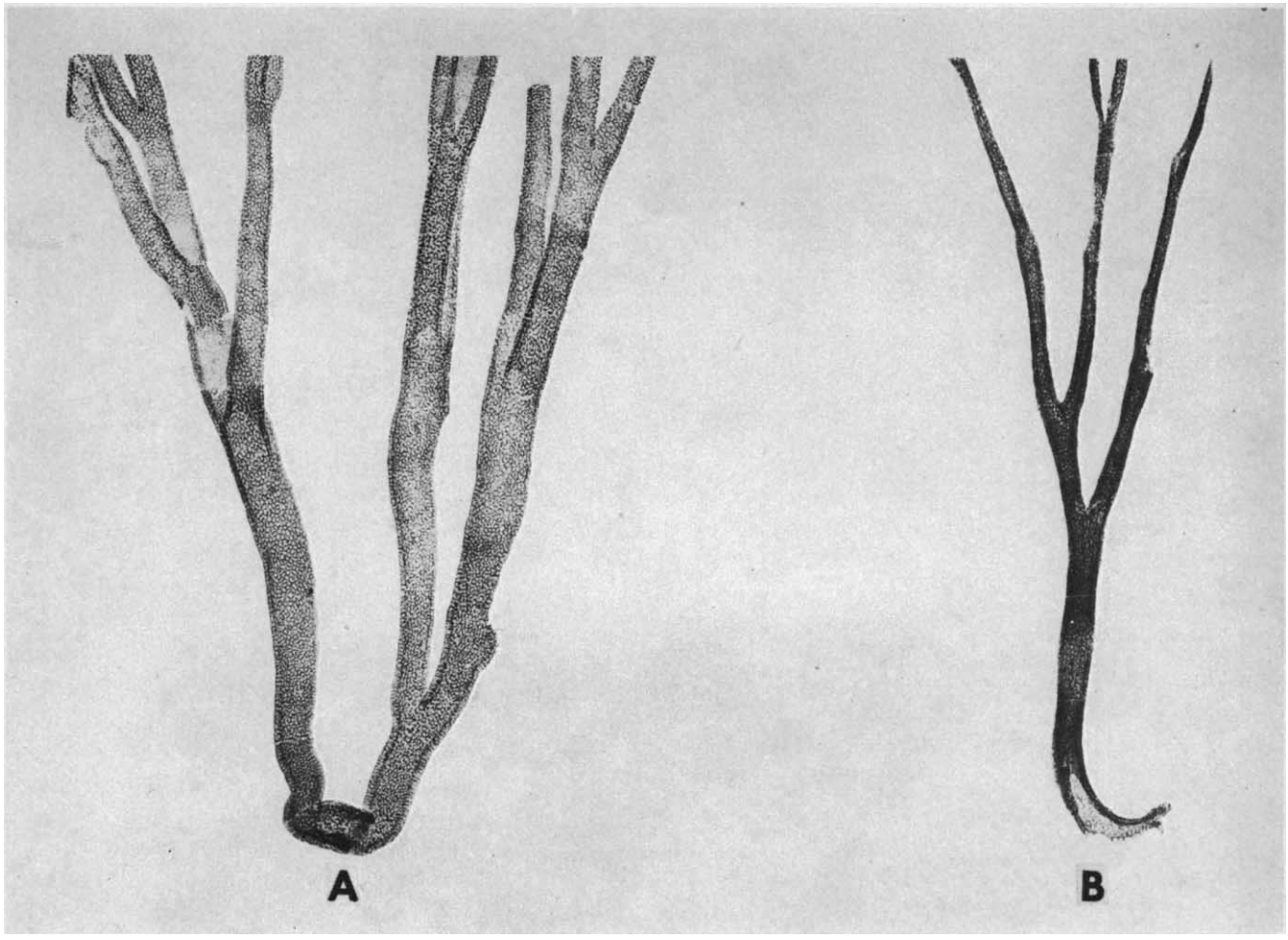

Fig. 7. *Mosaic photomicrographs of comparable portions of collecting system dissected from test and control kidneys of MD379; duration of ligation, seven days (reduced to ×62 from ×200).* Collecting system *A* presents marked, diffuse rather symmetrical dilatation, and stands out in contrast to collecting system *B*, representing control.

an early stage. Examples of this same appearance in control fetal rabbits from our material (Fig. 9) illustrate this point. It is believed that this thickening may represent a propensity for growth activity somewhat greater than that elsewhere in the nephron. It may be that the bend of the loop is a "weak spot."

Again, one wonders about the situation in renal cystic diseases in man. Are cysts of the loop of Henle, and particularly of the bend of the loop, common in microdissected human material? The answer is *yes*. In the series of articles by Osathanondh and Potter [9, 11–14], presenting the results of microdissection studies in a wide variety of human renal cystic disease, it is readily apparent that cysts of Henle's loop are commonplace. Of a total of 18 mosaic photomicrographs of microdissected renal units illustrating these articles, 13 display cysts of the loop of Henle, in most instances confined to the bend of the loop. The cysts of Henle's loop were not necessarily the only cysts present in these illustrations, there being portrayed many cysts in other portions of nephron or in collecting ducts. The cysts of the loop of Henle are repeatedly referred to in the text of these articles. In dissections of examples of the type 1 polycystic kidney in their classification [11], Osathanondh and Potter found cysts at the "angle" of the loop of Henle in 30% of the nephrons. In the variety of cystic kidney designated by them as type 2 [12], they describe "small focal dilatations occasionally present, especially involving Bowman's capsule and the angle of Henle's loop." In the type 3 cystic kidney of the Osathanondh and Potter classification [13], the authors found cysts in all portions of the nephron, but noted that Bowman's space and the angle of the loop of Henle are most commonly involved. The cysts encountered in the kidneys of the nine adults in this group were noted to be larger than those in the newborn infants, but they were of the same distribution and configuration, and

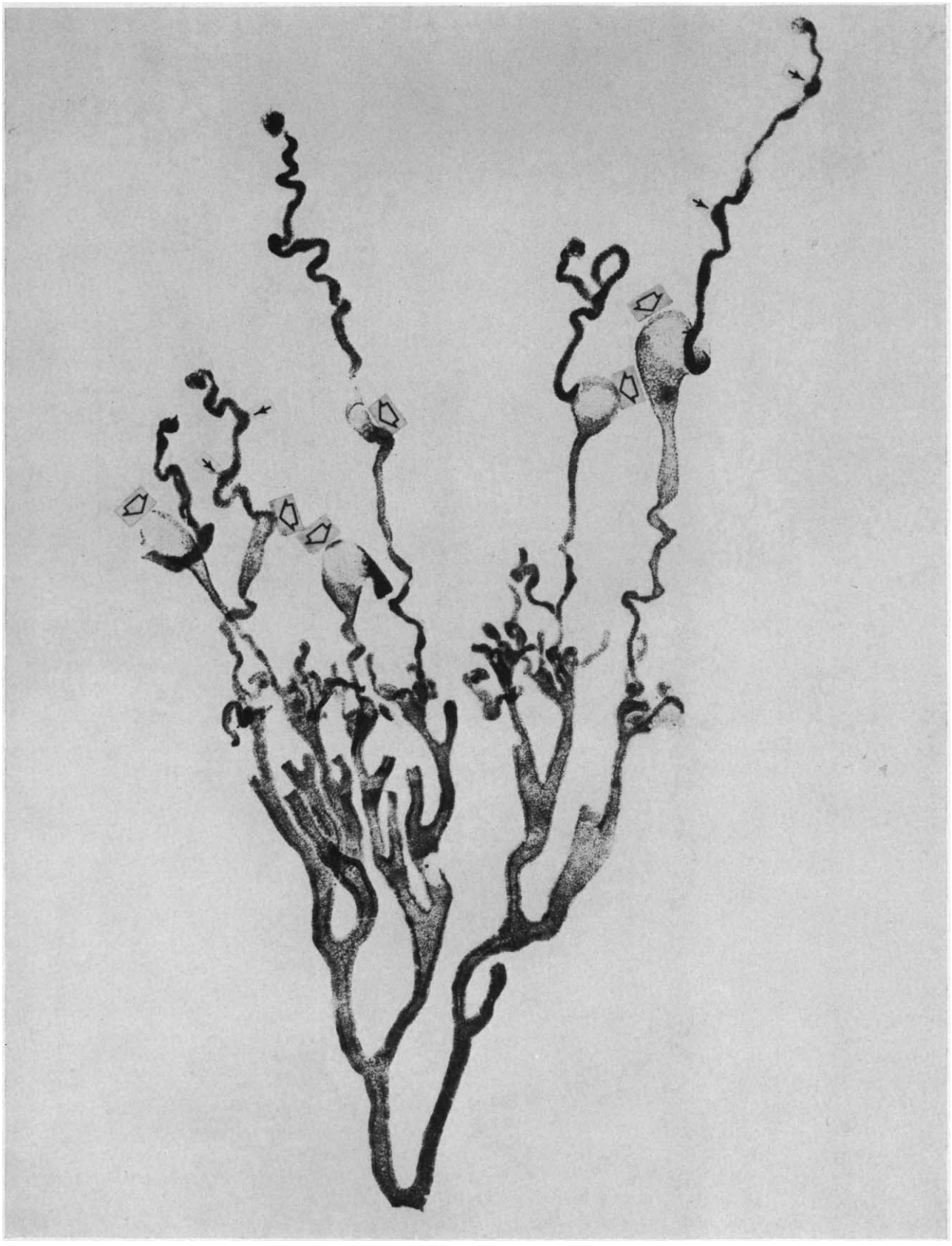

Fig. 8. *Mosaic photomicrograph of dissected material including a portion of collecting system with some of nephrons still attached to most distal branches of ducts (reduced to* $\times 50$ *from* $\times 200$*).* At least two proximal tubules present "minimal change" (*arrows*). (From test kidney MD373; duration of ligation, four days). At least five nephrons present cysts of the bend of the loop of Henle. Bends are marked by *open arrows*. The nephrons have been straightened for reasons of display.

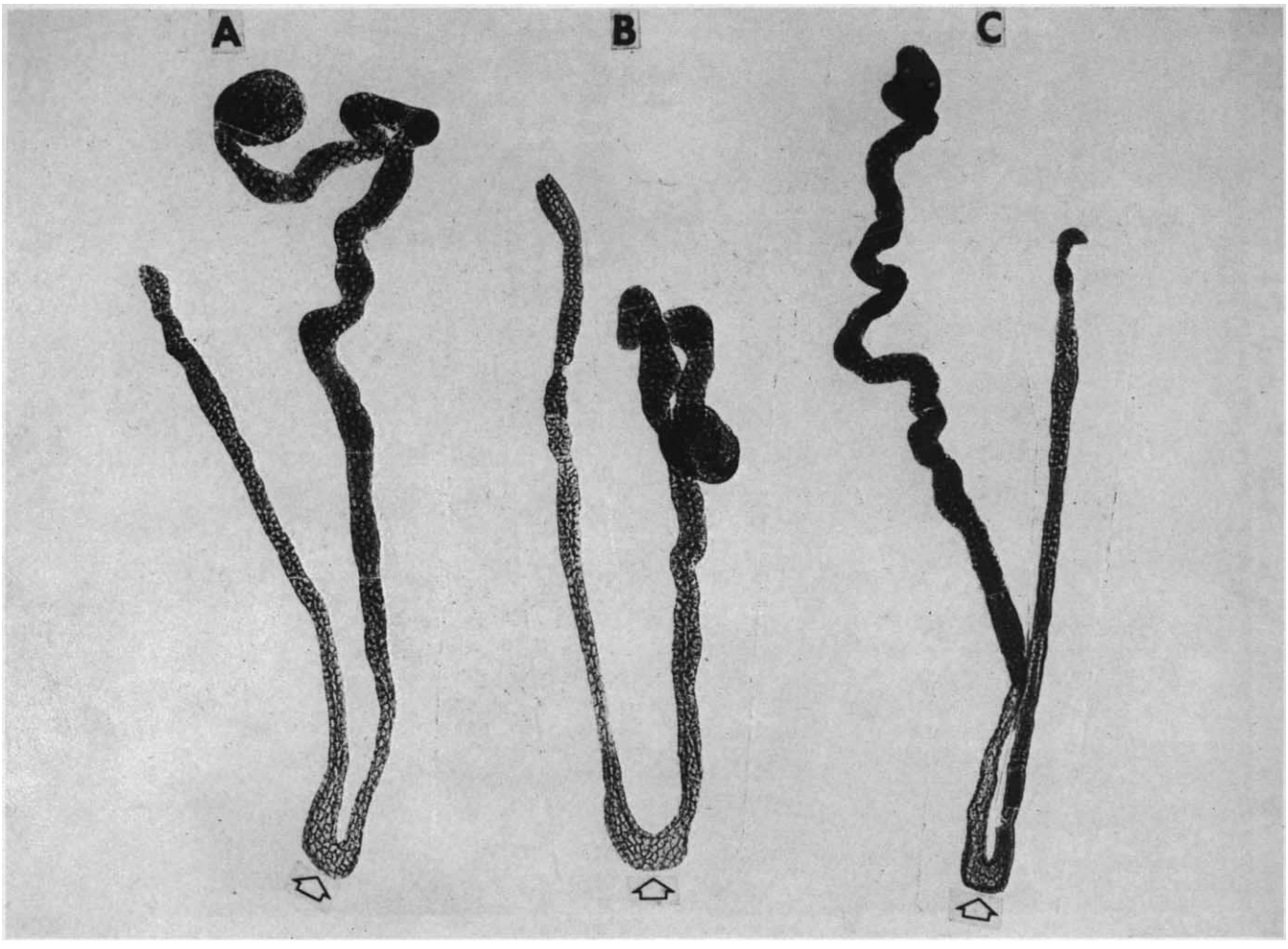

Fig. 9. *Mosaic photomicrographs of three nephrons dissected from control kidney MD377 (reduced to × 114 from × 200).* Each presents a localized bulge at the bend or angle of Henle's loop. Again, bends are indicated by *open arrows.*

included cysts of the loop of Henle. In the group of cystic kidneys which Osathanondh and Potter designated as type 4 [9] (due to urethral obstruction), these authors also noted the presence of cysts in, or dilatation of, Henle's loop or, specifically, the angle of Henle's loop.

The publications of Baxter [15–17] are another source of microdissected material from cystic kidneys. In six of the 25 kidneys in the series, cysts of the "crest of Henle's loop" were encountered, and in nine, cysts of the "apex of Henle's loop (junction with distal tubule)" were noted. Two of the nine were also included in the group of six that displayed cysts of the "crest" of Henle's loop. Thus, a total of 13 kidneys displayed cysts involving one or more portions of the loop of Henle. Four of the patients from whose kidneys cysts of the loop of Henle were dissected also displayed cystic disease of bile ducts. All of the 13 patients displaying cysts of Henle's loop were newborn or premature.

It is evident from our microdissection studies that in the fetal rabbit ureteral obstruction may be followed not only by marked dilatation of collecting ducts but also by the formation of cysts of the nephrons, particularly of the loops of Henle. It is also evident from the literature that such cysts are present commonly, in large numbers, in a variety of human renal cystic diseases.

The pathogenesis of such cysts in human kidneys under conditions of urinary obstruction, particularly in the fetal or newborn period, presents no serious conceptual problems. One might readily concede that the cysts are likely to form in either lapine or human kidneys in response to urinary back pressure imposed in fetal life. The susceptibility of the bend of the loop of Henle in both species is likely on a common basis, i.e., growth potential and anatomic configuration.

The occurrence of a high percentage of cysts of the bend of the loop of Henle in infantile polycystic disease (Osathanondh–Potter type 1) cannot be

explained on ureteral or urethral obstruction. It is possible, however, that the large hyperplastic cysts of interstitial collecting ducts which dominate the picture in this kind of renal cystic disease may cause local obstruction of individual nephrons by contiguous pressure, leading to the formation of nephronic cysts, including those of Henle's loop. Similar theoretical considerations may be applied to the other forms of renal cystic disease in which cysts of Henle's loop are common, but in which obstructions of urinary tract may not be demonstrable.

Acknowledgments

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